# Neuroprotective role of zingerone: Investigation the effective doses of zingerone in lead acetate-induced brain dysfunctions in rats


## Abstract

This experiment were design to determine the effective dose of zingerone against sublethal dose of lead acetate that induced-brain dysfunctions in rats, through using different successive doses of zingerone on some parameters related to oxidative stress for 28 days. Thirty six adult male rats were randomly selected and divided equally into six experimental groups and treated for 28 days as the follows: Control group administrated sterile distilled water and G1, G2, G3, G4, and G5 groups of rats' gavage following dose as respectively; 25, 50, 100, 150, 200 mg/kg. B.W. orally of zingerone and sublethal dose (1/280 from $LD_{50}$) of lead acetate administrated orally to all groups. Blood samples were collected at the end of the experiment for measuring the serum malondialdehyde, neuroglobulin and dopamine concentrations. The result showed a significant ($P<0.05$) positive correlation between successive doses of zingerone and dopamine and neuroglobulin concentrations, while a significant ($P<0.05$) negative correlation between successive doses of zingerone and the concentration of malondialdehyde in all animals which are treated with lead acetate comparing to control group. Concluded from this research show that the zingerone has a potent antioxidants and neuroprotective effects at the dose 125 mg/kg BW may result in a significant improvement of the neurotransmitters levels and decrease in the production of oxidative stress to the brain tissue.



**Keywords**: Brain damage, Effective dose, Neurodegenration diseases, Oxidative stress, Zingerone.


## Introduction

Zingerone is a nontoxic and inexpensive compound with varied pharmacological activities. It is the least pungent component of *Zingiber officinale*. Zingerone is absent in fresh ginger but cooking or heating transforms gingerol to zingerone. Zingerone closely related to vanillin from vanilla and eugenol from clove. Zingerone has potent antiinflammatory, antidiabetic, antilipolytic, antidiarrhoeic, antispasmodic, and so forth properties. Besides, it displays the property of enhancing growth and immune stimulation. It behaves as appetite stimulant, anxiolytic, antithrombotic, radiation protective, and antimicrobial. Also, it inhibits the reactive nitrogen species which are important in causing Alzheimer's disease and many other disorders (1, 2).

Ginger is a source of a large number of antioxidants and also plays an important role in the reduction of the lipid oxidation and inhibits the pathogenesis of diseases. Previous study reported that ginger extract possesses antioxidative characteristics and shows a role in

scavenge superoxide anion and hydroxyl radicals (3) and gingerol, inhibited ascorbate/ferrous complex induced lipid peroxidation in rat liver microsomes (4). Additionally, a fraction of the dried ginger powder abundant in polyphenols showed high antioxidant activity based on data from FRAP, oxygen radical absorbance capacity, and cellular antioxidant activity assays (5).

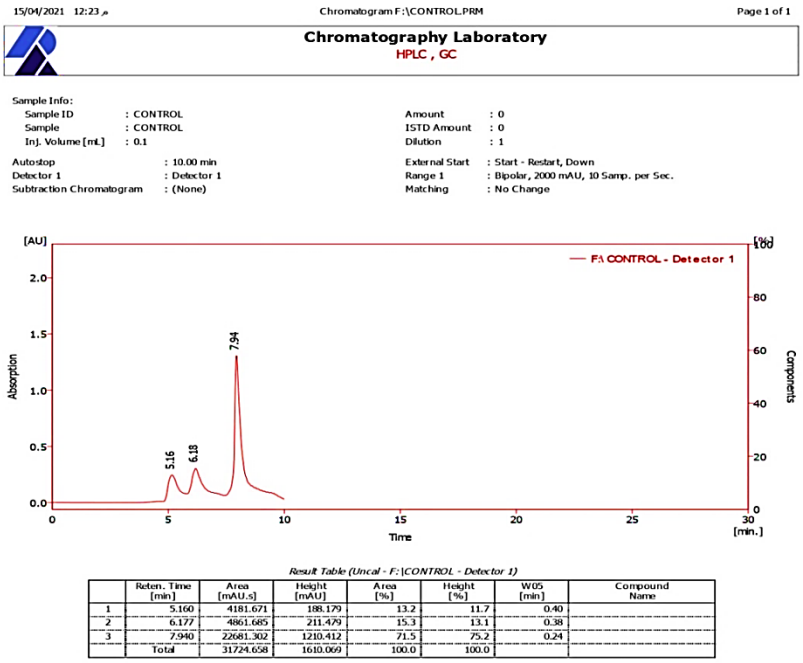
Several studies have indicated that ginger was effective for protection against oxidative stress. The underlying mechanisms of antioxidant action were investigated in cell models (6). Ginger extract showed antioxidant effects in human chondrocyte cells, with oxidative stress mediated by interleukin-1β (IL-1β). It stimulated the expression of several antioxidant enzymes and reduced the generation of ROS and lipid peroxidation (7). Additionally, ginger extract could reduce the production of ROS in human fibrosarcoma cells with $H_2O_2$-induced oxidative stress (8). Recently, many investigations have revealed that ginger positively affects memory function and exhibits anti-neuroinflammatory activity, which might contribute to the management and prevention of neurodegenerative diseases (9).

Further experiments in mouse hippocampi and rat C6 glioma cells revealed that ginger extract promoted the formation of synapses in the brain through the activation of extracellular signal-regulated kinase (ERK) induced by nerve growth factor (NGF) and cyclic AMP response element-binding protein (CREB) (10). Another study found that 6-shogaol exhibited neuroprotective activity by activating Nrf2, scavenging free radicals, and elevating the levels of several phase II antioxidant molecules, such as NQO1 and HO-1, in neuron-like rat pheochromocytoma PC12 cells (11). The aim of the present study is to determination the effective dose of zengeron supplement as a natural antioxidant on the modulation of toxic effects and oxidative stress induced by sublethal dose of lead exposure in rats.

## Material and methods

### Zengerone supplement

The ginger powder that used in this study comes from ginger rhizomes from controlled organic cultivation in India. Naturally, no pesticides were used during the cultivation process. Each capsule is free from any sort of additives including gelatin, making the product suitable for vegans, as shown in HPLC analysis (figure 1) with following specifications: 450 mg organic ginger powder per capsule, 100% certified organic ginger, 180 capsules/ bottle, 100% vegan, Made in Germany, Free from additives, pesticides, non-GMO, Produced according to ISO 9001, HACCP, GMP standards**.**




Picture -1. Chromatographic study

**Experimental design**

Forty adult male rats, weighed 190-220 gm. were used and housed in an animal house (College of Veterinary Medicine/ Baghdad University). The animals were kept at 22 -25˚C, with 12h light/dark cycle. Animals were allowed freely access to water and pellets along the experimental period. After acclimatization for 15 days, will be randomly selected and divided equally into sex experimental groups and treated for 28 days as the follows: Control group administrated sterile distilled water and G1, G2, G3, G4, and G5 group of rats gavage dose as following respectively; 25, 50, 100, 150, 200 mg/kg. BW of Zingerone and sub-lethal (1/280 from $LD_{50}$) of lead acetate to all groups. Blood samples will be collected at the end of the treatment for measuring the following criteria: Serum malondialdehyde (MDA); the level of serum MDA was determined by a modified procedure described by (12), the serum neuroglobulin and dopamine concentration (pg/mL) was measured by using the commercially available ELISA Kit (CEA851Ge, Cloud-Clone Corp Com. USA) according to the manufacturer's instructions.

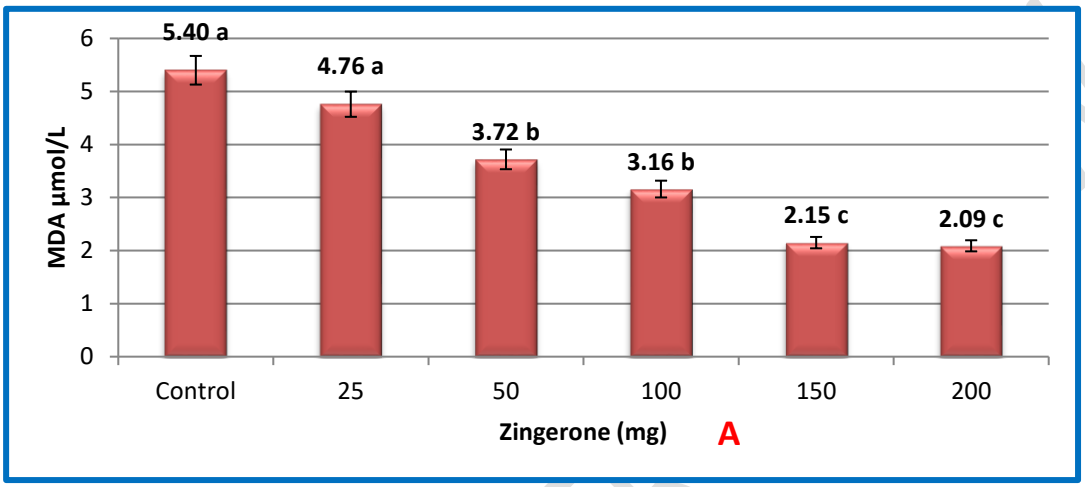
**Statistical analysis**

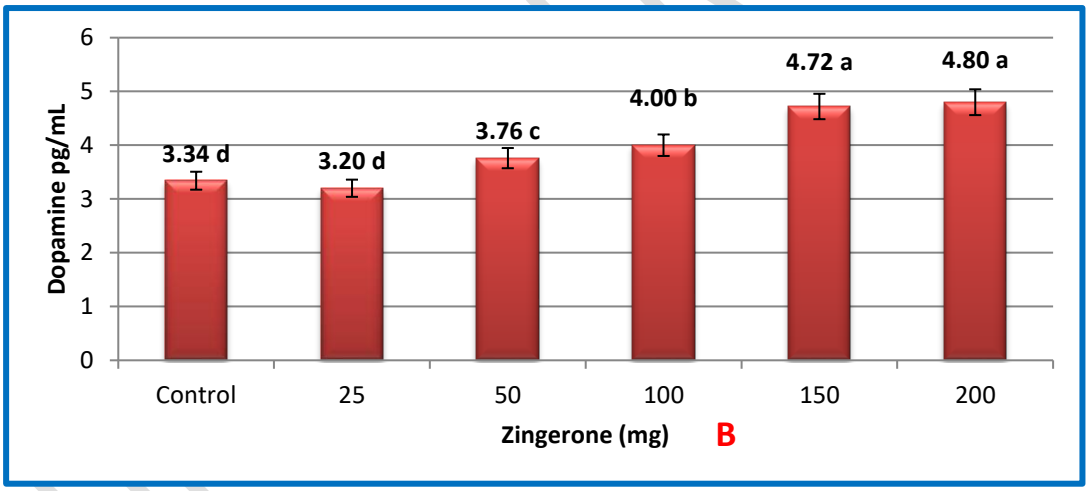
Data was performed using SAS (Statistical Analysis System - version 9.1). One-way ANOVA and least significant differences (LSD) post hoc test were performed to assess significant differences among means. $P < 0.05$ is considered statistically significant (13).

**Results**

The results shown in figure 1 (A, B, and C) after treatment of rats with zingerone supplement (25, 50, 100, 150, and 200 mg/kg B.W.) against LD50 of lead acetate (1/280 from rats in the previous experiment) for 28 days. A significant ($P<0.05$) decrease is shown in MDA concentration (figure 1-A) with successive zingerone supplement doses in all treated groups, while there was no differences noticed between G1 (25 mg) and control, between G2 (50 mg) and G3 (100 mg) and between G4 (150 mg) and G5 (200 mg). The data in figure 1-B showed

a significant (P<0.05) increase in the concentration of dopamine concomitant with zingerone supplement dose increase. Besides, the results showed no-significant (P>0.05) differences between G1 (25 mg) and control and between G4 (150 mg) and G5 (200 mg), while there was a significant differences between G2 (50 mg) and G3 (100 mg). Concerning neuroglobine, figure 1-C showed no-significant (P>0.05) increase in neuroglobine concentration in, G1, G2 and G3 rats treated with zingerone supplement against sub lethal dose of lead acetate (1/280 from LD50 of PbAc) comparing to control. There is a significant increase in neuroglobine concentration related to zingerone dose increase in G4 (150 mg) and G5 (200 mg) treated groups comparing to control and other treated groups.



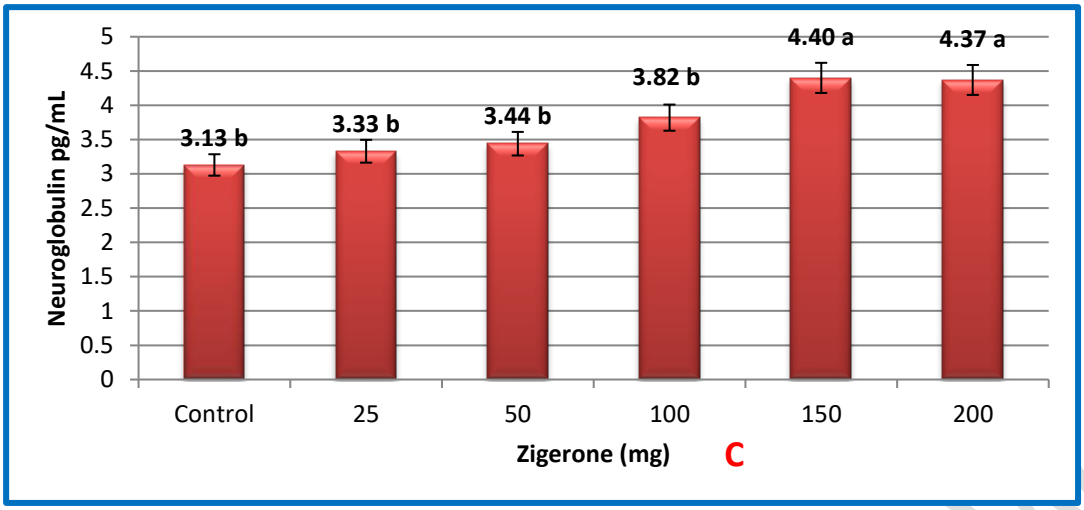
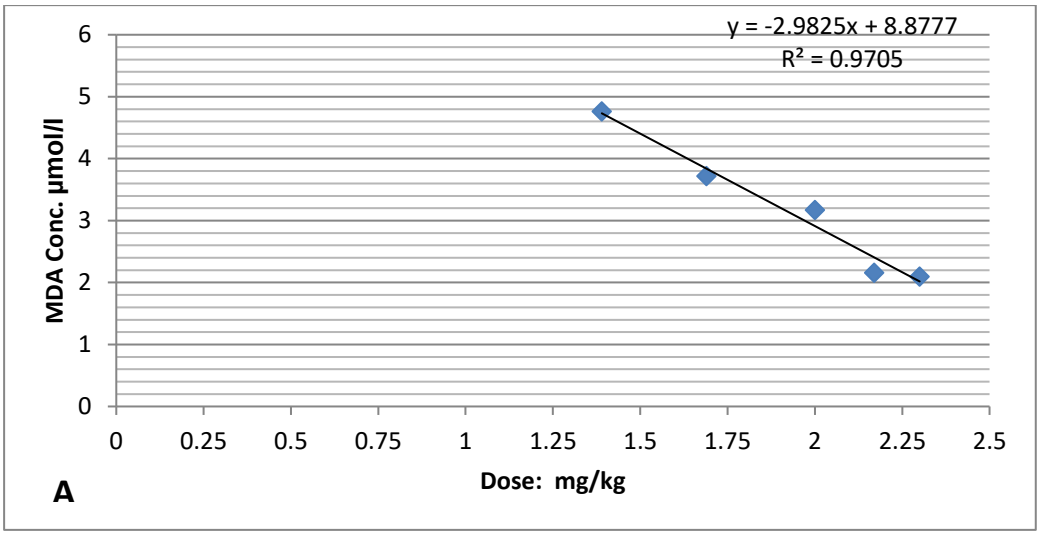
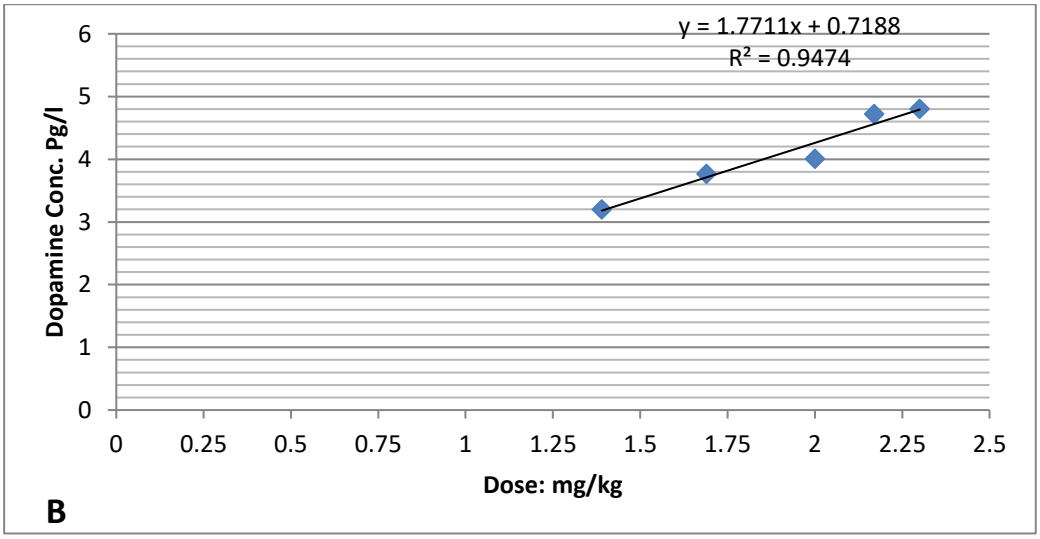



**Figure 1:** Shows the effect of different successive doses of zingerone supplement on MDA (Figure 1-A), dopamine (Figure 1-B) and neuroglobulin concentrations after 28 days in adult male rats.
Values are expressed as mean ±SE. n= 6. Small letters denote significant differences between groups (P< 0.05).

**Determination the effective dose (ED) of zingerone**

Depending on the results shown in figures 2 (A, B, and C) maximal significant changes in the above parameters were recorded after 28 days of zingerone supplement with sublethal dose (1/280 of $LD_{50}$) of Pb treated rats. Accordingly, the results shows the estimation of ED of zingerone as follows: Figure 2-A explained highly significant ($P<0.05$) decreases in serum MDA concentration accompanied by successive increase in the dose of zingerone supplement, Were the estimated of ED of zingerone was equal to 125 mg/Kg B.W., a positive relationship was observed between serum dopamine and neuroglobulin concentrations and successive doses of zingerone as show in figure 2 (B and C). To determine the ED of zingerone which obtained from the equations of straight line for the previous parameters, the arithmetic mean of ED of zingerone in rats received sub-lethal dose (1/280 of LD50) of Pb on serum MDA, dopamine and neuroglobulin concentrations which equal to 125 mg/kg BW according to probit analysis.



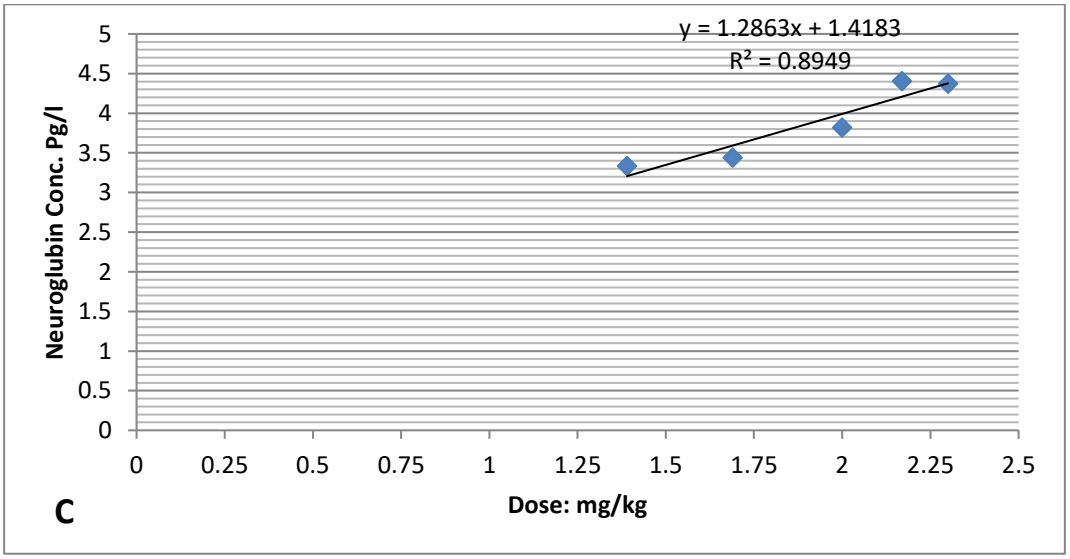




**Figure 2:** Reveals effect of different successive doses of zingerone supplement on serum MDA (A), dopamine (B) and neuroglobuline (C) concentrations after 28 days in rats . n= 6, ED= 125 mg / kg, BW.

**Discussion**

Administration of zingerone ED with lead acetate sub lethal dose 1/280 of LD50 showed a significant decrease in serum MDA concentration at dose 125 mg/kg B.W. according to probit method, as compared with lower and higher doses, these results were in agreement with. (14) and (15) whom reported that ginger suppresses lipid peroxidation and recovered antioxidant concentration. Also (16) found that ginger, significantly lowered LPo by maintaining the activities of antioxidant enzymes such as SOD, catalase and glutathione peroxidase (GPx) in rats. So, current results confirm the ability of zingerone to reduce the oxidative stress induced by PbAc exposure (17, 18).

The result that showed a significant increase in the concentrations of dopamine and neuroglobine in treated groups that indicate the zingerone supplement work on the neurons functions improvement and inhibits the neurodegeneration disorders. The results are going in line with (19) who reported a neuroprotective effect of ginger through protecting dopaminergic cells via the inhibition of neuroinflammatory responses of microglia (20) suggested that 6-shogaol may play a role in inhibiting glial cell activation and reducing memory impairment. It have been suggested that ginger crude extract might be a potential neuroprotective agent for the treatment of lipopolysaccharide (21) and monosodium glutamate (MSG)-induced neurodegenerative diseases (22), due to polyphenolic compounds content of ginger. Ginger has a high antioxidant activity to inhibit the hydroxyl radicals, due to the presence of bioactive phytochemicals like zingerone gingerols, shogaols, paradols and gingerdiols. Zingerone superoxide anion scavenges peroxyl radicals and also inhibits the production of NO; it is the major bioactive constituent responsible for the antiinflammatory and antioxidant activities of ginger (23, 24). It seems that ginger, given its antioxidant, immunomodulatory and anti-inflammatory capacity, has the ability to intercept all the main elements involved in the development of multiple sclerosis as well as to attenuate the symptoms of neurological diseases (25, 26). The prophylactic role of ZS against the oxidative stress caused by sub lethal dose of PbAc, counteracts the progression of neurodegenerative diseases. These result are in agreement with (27) who showed that ginger can be a candidate to treat neurodegenerative diseases through bioactive compounds and may improve neurological symptoms and pathological conditions by modulating cell death or cell survival signaling molecules. Collectively, our findings may be helpful in understanding the modulation of brain injury under lead acetate toxicity, zingerone are considered is a promising edible option for reducing the deleterious effects of lead due to its strong antioxidant and modulatory capabilities.

**Conclusions**

zingerone has a potent antioxidants and neuroprotective effects at the dose 125 mg/kg BW may result in a significant improvement of the neurotransmitters levels and decrease in the production of oxidative stress to the brain tissue.

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